UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/694,519	10/23/2000	Robert Joseph Isfort	8311	9641

27752 7590 12/22/2003

THE PROCTER & GAMBLE COMPANY
INTELLECTUAL PROPERTY DIVISION
WINTON HILL TECHNICAL CENTER - BOX 161
6110 CENTER HILL AVENUE
CINCINNATI, OH 45224

EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	20

DATE MAILED: 12/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/694,519	ISFORT ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16-26 and 28* is/are pending in the application.

4a) Of the above claim(s) *1-14,18-26 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16* is/are rejected.

7)☒ Claim(s) *17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This office action is in response to an amendment filed on August 27, 2003. Claims 1-28 were previously pending, with claims 1-14, 18-26 and 28 withdrawn from consideration. Applicants cancelled claims 15 and 27, and amended claims 16 and 17. Claims 1-14, 16-26 and 28 are pending, with claims 1-14, 18-26 and 28 withdrawn from consideration. Claims 16 and 17 will be examined.

2. Applicants' amendments and claim cancellations rendered moot the following rejections: rejection of claims 15, 17 and 27 under 35 U.S.C. 112, first paragraph (enablement); rejection of claims 16, 17 and 27 under 35 U.S.C. 112, second paragraph; rejection of claim 15 under 35 U.S.C. 102 (b) over Gourlet et al., and rejection of claims 16, 17 and 27 under 35 U.S.C. 102 (b) over Vittone et al. Rejection of claim 16 under 35 U.S.C. 112, first paragraph (enablement) is maintained for reasons given in the "Response to Arguments" section. The rejection is re-stated in view of Applicants' amendments and arguments.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on August 27, 2003 was filed after the mailing date of the non-final office action on March 24, 2003. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

4. Applicant's arguments filed on August 27, 2003 have been fully considered but they are not persuasive.

Regarding the rejection of claim 16 under 35 U.S.C. 112, first paragraph (enablement), Applicants argue that the amended claim 16 is enabled because:

a) positive effects observed by binding of $VPAC_1$ receptor agonists on $VPAC_2$ receptors may be explained by higher amounts of $VPAC_1$ agonists used (page 10 of the response, second paragraph),

b) positive effects seen with non-specific agonist PACAP-38 are explained by the fact that it binds to $VPAC_2$ receptors, and "It is possible that unusually high local concentrations of an agonist that is not $VPAC_2$ receptor-specific may nevertheless lead to $VPAC_2$ receptor activation" (page 10 of the response, second paragraph),

c) it is well established in the art that both pancreas and skeletal muscle express $VPAC_2$ receptors but they do not express either $VPAC_1$ receptors or PACAP-Type 1 receptors, therefore the effects seen in the muscle are due to binding to the $VPAC_2$ receptor (page 10 of the response, third paragraph),

d) identifying agonists specific for $VPAC_2$ receptors is routine experimentation (page 13 of the response, second paragraph),

e) specification teaches how to use $VPAC_2$ receptor agonists to treat skeletal muscle atrophy using cell-free and cell-based assay systems, including animal models of muscle atrophy (page 13 of the response, last paragraph; page 14, first paragraph),

f) specification provides examples of how to treat rats and mice with VPAC receptor agonists (page 14, second paragraph),

g) muscle tissue expresses only $VPAC_2$ receptors but they do not express either $VPAC_1$ receptors or PACAP-Type 1 receptors (page 15, second paragraph).

Applicants amended claims 16 and 17 to read on $VPAC_2$ receptor agonist, rather than broadly on any VPAC receptor agonist. However, this amendment does not provide enablement for all of the $VPAC_2$ receptor agonists, for the following reasons. If a compound binds to the receptor

and activates it, it is a receptor's agonist. Therefore, since Applicants did not define what IC_{50} and /or ED_{50} makes a compound "specific" for one type of receptor and non-specific for another type, basically any compound which binds to $VPAC_2$ receptor and activates it, can be considered to be a $VPAC_2$ receptor agonist. Regarding Applicants' arguments listed as a), b) c) f) and g), they appear to contradict each other and Applicants' own data. For example, Applicants argue that only $VPAC_2$ receptors are expressed in skeletal muscle, while providing evidence in the form of the publication of Wei et al. (J. Neuroendocrinology, vol. 8, pp. 811-817, 1996; cited in the currently submitted IDS), showing that a new type of receptor (named PACAP/VIP R2), which binds both VIP and PACAP peptides (PACAP-38 and PACAP-27), is also found in skeletal muscle (see, for example, Figure 3). According to Applicants' terminology, this is the $VPAC_1$ receptor (see page 13 of the specification, line 13). Therefore, the action of PACAP-38 may be mediated through this receptor, rather than through the $VPAC_2$ receptor. In addition, Applicants did obtain significant results with the PACAP-38 agonist.

Therefore, while Applicants are enabled for a method of increasing a skeletal muscle mass or function in a subject by administering to the subject a safe and effective amount of $VPAC_2$ receptor agonists PACAP-38 or Ro 25-1553, no enablement is provided for any other $VPAC_2$ receptor agonists. The rejection is maintained.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for VPAC (vasoactive intestinal peptide) receptor agonists specific for $VPAC_2$ (Ro

25-1553) or both $VPAC_1$ and $VPAC_2$ receptors (PACAP-38, pituitary adenylate cyclase-activating polypeptide), does not reasonably provide enablement for any other agonists $VPAC_2$ receptor agonists. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants described using the following VPAC receptor agonists to counteract muscle atrophy in mice: [K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], Ro 25-1553 and PACAP-38. The specification does not provide any indications that VPAC receptor agonists such as VIP (vasoactive intestinal peptide), PACAP-27, helodermin, peptide histidine isoleucine amide (PHI), peptide histidine methionine amide (PMI), peptide histidine valine amide (PVI), growth hormone releasing hormone (GHRH, GRH, GRF), secretin, glucagon, (Arg15, Arg21) VIP, [Arg 15,20,21, Leu17]-VIP-Gly-Lys-Arg-NH_2, multimeric VIP fusion protein, Ro-1392 and PACAP(6-38), when administered to a subject, would result in an increase of the skeletal muscle mass or function.

The agonists of VPAC receptors listed above are related to VIP, whose receptors are widely distributed in the central and peripheral nervous system and in plasma membranes of many organs and tissues (gastrointestinal tract, lung, heart, uterus, adrenal, adipocytes, enterocytes, hepatocytes, liver, etc.). VIP has a broad range of biological actions, such as vasodilation of vessels, brochodilation, relaxation of various muscles (esophageal sphincter, fundic muscle, gallbladder smooth muscle, colonic smooth muscle of the intestines), glycogenolysis and lipolysis, bone resorption, release of insulin, glucagon, or somatostatin in the pancreas, stimulation of prolactin, growth hormone (GH) release in the pituitary, etc. (Said, J. Endocrinol. Invest., vol. 9, p. 191-200, 1986).

In addition, helodermin, glucagon, GRF, secretin have their own specific receptors, but also bind to the VIP receptors. For example, secretin, GRF, PHI and helodermin bind to the VIP

receptor, VIP, GRF, PHI and helodermin bind to the secretin receptors (in pancreas and exocrine cells), glucagon binds to its receptors in the liver, and GRF to its receptors in the pituitary gland (Laburthe et al., Ann. NY Acad. Sci., vol. 527, pp. 296-313, 1988, see Fig. 9). GRF and PHI were found to be VIP receptor agonists (Emami et al., Peptides, vol. 7, pp. 121-127, 1986, see Abstract), and PHM was found to be a VIP agonist with low potency on human VIP receptors (Laburthe et al., Life Sci., vol. 36, pp. 991-995, see Abstract).

PACAP-38 and PACAP-27 in addition to binding to their own receptors bind to the VIP receptors (Ulrich et al., Gastroenterology, vol. 114, pp. 382-397, 1998, see page 387, third paragraph).

Therefore, taking all of the above facts into account, administration of any of the above VPAC agonists, despite the fact that they are related, cannot be predicted to have an effect of increasing muscle strength or function, and may potentially lead to harmful outcome, as they also target other receptors. As noted by Musso et al. (U.S. Patent No. 4,835, 252): " ...the naturally occurring VIP has so many biological activities that its use is limited, because beneficial effects are associated unavoidably with significant, deletorious side effects, especially when the VIP is administered intravenously..." (col. 2, lines 27-31).

Due to the large quantity of experimentation necessary to establish whether the administration of compounds other than Ro 25-1553 and PACAP-38 would result in an increase of muscle mass or function, the lack of direction/guidance presented in the specification regarding administration of compounds other than Ro 25-1553 and PACAP-38 resulting in an increase of muscle mass or function, the lack of working examples directed to the administration of compounds other than Ro 25-1553 and PACAP-38 and resulting increase of muscle mass or function, the complex nature of the invention (agonist binding to several receptor types), the unpredictability of

the effects of the administration of compounds other than Ro 25-1553 and PACAP-38 on an increase of muscle mass or function (see discussion above), undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

7. No references were found teaching or suggesting claims 16 and 17. Claim 16 is rejected for reasons given above. Claim 17 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

The examiner will move to the new office in Alexandria on January 8, 2004. The new phone number in that office is (571) 272-0789. Gary Benzion will move to the new office on January 22, 2004. His new phone number is (571) 272-0782.

TS
December 18, 2003

JEFFREY FREDMAN
PRIMARY EXAMINER